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限时饮食可能是改善精神分裂症患者代谢的新兴干预措施

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摘　要

精神分裂症患者常存在显著代谢紊乱，这不仅严重影响患者的生活质量和治疗依从性，还增加了患者过早死亡的风险。生活方式干预往往是改善代谢紊乱的一线疗法，限时饮食则是一种基于昼夜节律的新兴饮食干预措施。动物研究和人类研究均显示限时饮食具有有益的代谢作用，不仅可以减轻体重，还有益于心脏代谢健康。精神分裂症和抗精神病药物引起代谢紊乱的机制和限时饮食产生有益代谢作用的机制之间存在较多的关联，所以限时饮食可能可以帮助精神分裂症患者改善其代谢问题。因此，本文主要对精神分裂症患者的代谢问题以及限时饮食的应用效果和作用机制进行综述，希望为限时饮食未来应用于精神分裂症患者以帮助他们改善代谢提供参考。

关键词

精神分裂症，抗精神病药物，限时饮食，代谢

Time-Restricted Feeding May Be a New Intervention to Improve Metabolism of Schizophrenia Patients

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Abstract

Schizophrenia patients often have significant metabolic disorders, which not only seriously affect their quality of life and treatment compliance, but also increase the risk of premature death. Lifestyle intervention is often the first-line treatment to improve metabolic disorders, while time-restricted feeding is a new dietary intervention based on circadian rhythm. Animal studies and human studies have shown that time-restricted feeding has beneficial metabolic effects, which can not only reduce weight, but also benefit the cardiometabolic health. There are many correlations between the mechanism of metabolic disorder caused by schizophrenia and antipsychotic drugs and the mechanism of beneficial metabolic effect caused by time-restricted feeding. Therefore, time-restricted feeding may help schizophrenia patients improve their metabolic problems. Therefore, this paper mainly reviews the metabolic problems of schizophrenic patients and the application effect and mechanism of time-restricted feeding, hoping to provide reference for the future application of time-restricted feeding to schizophrenic patients to help them improve metabolic problems.

Keywords

Schizophrenia, Antipsychotic Drugs, Time-Restricted Feeding, Metabolism

1. 引言

近年来，人们越来越关注精神分裂症患者的过早死亡问题。研究发现精神分裂症患者的预期寿命降低了 20 多年[1]。澳大利亚和美国进行的大规模队列研究也证实了这种过早死亡的风险增加[2] [3]。数十年来，已有研究表明精神分裂症患者存在显著代谢紊乱，包括体重增加、肥胖、糖代谢和脂代谢异常等[4] [5]，这些严重的不良反应对生活质量具有毁灭性的影响，并且是严重躯体并发症(包括心血管疾病、中风和过早死亡)的主要风险[6] [7] [8]。体重增加还会加剧患者对自己的负面看法，并且是治疗依从性差的一个因素，会使患者再住院的风险增加 5 倍[9] [10] [11]。

英国国家卫生和临床医疗优选研究所(National institute for Health and Care Excellence, NICE)出版的成人精神病与精神分裂症治疗及管理指南(CG178) [12]和超重和肥胖儿童、青年人以及成人的识别评估和管理指南(CG189) [13]均建议将生活方式干预作为超重或肥胖者的初始方法。生活方式干预措施，包括饮食改变、减少热量摄入和增加运动，已成为抵抗超重、肥胖和代谢疾病的第一线疗法。越来越多的研究表明，生活方式干预对接受抗精神病药物治疗的人有效[14] [15]。但是，这些生活方式的改变需要不断关

注营养素的质量和数量以及身体活动，他们的成功仅限于一部分人。因此，迫切需要新颖的干预措施。

营养的质量和数量是公认的健康决定因素。然而，昼夜节律领域中的最新进展发现一天中摄取食物的时间会影响体重、身体组成、葡萄糖调节、脂质稳态、肠道微生物组、心脏功能、炎症、睡眠和整体健康等[16] [17]。限时饮食(Time-restricted feeding, TRF) [18]即是在此背景下出现的一种新兴的饮食干预措施，是指每天将饮食窗口限制在指定的小时数内(小于 12 小时)，并在一天的剩余小时内禁食(允许零卡路里的饮料)，旨在维持一致的每日进食和禁食周期，以支持强劲的昼夜节律。在摄食窗口期间，不需要个人以任何方式计算卡路里或监控食物的摄入量。所以，限时饮食实施起来较为简便，可以纳入日常生活方式，同时可以长期坚持。这些特征使限时饮食与其他禁食方案相比更加不同且更为现实，可能是控制体重和改善精神分裂症患者代谢紊乱的有前景的治疗策略。

限时饮食在动物模型中已开展了多项研究。既往在啮齿动物和果蝇中进行的限时饮食研究显示出有益的健康效果，包括降低胆固醇，空腹血糖，体重，体脂，炎症，同时改善能量消耗，睡眠质量和心脏健康功能等[19]。近 5 年来，研究者开始逐渐开展限时饮食的人类研究，显示出限时饮食具有减轻体重、改善心脏代谢健康等的有益作用。目前国外开展的限时饮食人类研究较多，而国内比较少。限时饮食的研究人群刚开始主要集中于正常体重受试者、超重或肥胖受试者，后来开始应用于糖尿病前驱期患者、代谢综合征患者以及冠心病患者。目前限时饮食尚未应用于存在代谢问题的精神障碍患者人群，所以尚无研究探索限时饮食对代谢紊乱的精神分裂症患者的干预效果。但是，精神分裂症和抗精神病药物引起代谢紊乱的机制和限时饮食产生有益代谢作用的机制之间存在较多的关联，所以限时饮食这种新兴的饮食干预措施，可能可以有效帮助精神分裂症患者改善其代谢问题。因此，本文主要对精神分裂症患者的代谢问题以及限时饮食的应用效果和作用机制进行综述，希望可以引起国内研究者对新兴的限时饮食的更多关注，并为限时饮食未来应用于精神分裂症患者以帮助他们控制体重、改善代谢以及探索可能的作用机制提供参考方向。

2. 精神分裂症患者存在显著代谢紊乱

精神分裂症患者本身可能存在潜在代谢风险。首次发作且未用药精神分裂症患者表现出不同程度的葡萄糖/脂质代谢以及代谢综合征相关方面的损害，表明系统性代谢紊乱与精神疾病之间存在复杂的联系[20] [21]。还有研究发现，精神分裂症本身与代谢综合征的倾向性较高相关[22]。

此外，大量证据表明抗精神病药的使用也会引起严重的代谢紊乱。二代抗精神病药，也称为“非典型抗精神病药”，目前是精神分裂症的一线治疗方法。尽管有报道称典型的抗精神病药会引起一定程度的代谢紊乱，但非典型的抗精神病药尤其是氯氮平和奥氮平会引起更严重的代谢副作用，包括体重增加、肥胖、高脂血症、胰岛素抵抗、高血糖和糖尿病[23] [24] [25] [26]。在开始抗精神病药物治疗后的 6~8 周内可以发现体重显著增加[6]。在精神分裂症首次发作的个体中，随访 1 年，有 65%的人体重增加了初始体重的 7%或更高[27]。对 78 项临床研究的 meta 分析发现，服用抗精神病药物的人中 35.3%表现出代谢综合征[28]。在诊断为代谢综合征的普通人群中，心血管疾病在 5~10 年内的相对风险约为两倍，而 2 型糖尿病的风险甚至增加了 5 倍[29]。

3. 精神分裂症和抗精神病药物引起代谢紊乱可能的机制

3.1. 引起代谢紊乱的中枢和外周机制

精神分裂症和抗精神病药物引起葡萄糖和脂质代谢紊乱的中枢和外周机制[30]。中枢神经系统(包括下丘脑等大脑中与代谢相关的脑区)接收来自周围器官的反馈，这些周围器官负责调节新陈代谢和食欲。同样，大脑中的代谢中心通过对周围器官(包括胃肠道、肝脏、胰腺、脂肪组织和骨骼肌)的作用来调节全

身的新陈代谢。这种反馈虽然不是连续的，但却是双向的，并且会产生细微的代谢平衡，这种平衡会受到精神分裂症固有的生物学变化的干扰，还可能受到抗精神病药物治疗的干扰。我们假设这些中枢和外周靶器官通过涉及多巴胺能、5-羟色胺能、组胺能和脂肪因子信号的共同分子信号网络相连。由于抗精神病药物会作用于这些信号系统的受体，因此这些药物可能具有协同作用，从而显著增加包括胰岛素抵抗和肥胖在内的代谢紊乱的风险。

3.2. 诱导肥胖和糖尿病的机制

抗精神病药物引起肥胖的机制被认为是在肥胖发展的早期阶段增加了食欲和食物摄入[24]。抗精神病药会拮抗 5-羟色胺 2C 受体、组胺 H1 和多巴胺 D2 受体，导致阿片－促黑素细胞皮质素原减少和神经肽 Y 产生增加，从而导致食欲增加，从而增加食物摄入量，导致肥胖[24] [31] [32] [33] [34] [35]。抗精神病药物诱导糖尿病可能的分子机制[36]：① 抗精神病药物可以抑制胰岛素敏感性细胞(如肌肉细胞、肝细胞和脂肪细胞)中的胰岛素信号通路，从而引起胰岛素抵抗；② 抗精神病药物引起的肥胖症可导致高水平的游离脂肪酸和炎症，间接引起胰岛素抵抗；③ 抗精神病药物可以直接损害胰岛 β 细胞，导致 β 细胞功能异常和凋亡。

3.3. 肠道微生物组的介导作用

在过去十年中，多项研究强调了肠道微生物组在肥胖症和糖尿病等代谢性疾病发展中的可能作用[37] [38]。考虑到肠道微生物组变化，体重增加和葡萄糖代谢之间的关联，抗精神病药物很可能通过改变人类肠道微生物组的组成，部分的介导代谢紊乱的发生[39]。Davey 等人[40]研究了奥氮平与抗生素共同给药对大鼠代谢参数和肠道微生物组的影响，发现用抗生素和奥氮平处理的大鼠的肠道厚壁菌门数量减少，拟杆菌门数量增加，而仅用奥氮平治疗的大鼠的厚壁菌门数量增加，拟杆菌门数量减少；此外，抗生素的共同给药减少了奥氮平治疗所导致的总体体重增加和子宫内脂肪堆积。人体的初步证据还表明肠道微生物组与抗精神病药物的使用及其代谢副作用有关。Bahr 等人[41]的研究发现服用利培酮的患者在治疗期间 BMI 显着增加，拟杆菌的比例更小。

4. 限时饮食的应用效果

4.1. 限时饮食的有益作用

4.1.1. 减少能量摄入和减轻体重

越来越多的证据表明，在随意摄入饮食情况下，限时饮食可能会自发地减少 20%~30%的能量摄入，会产生 1%~4%微小但有统计学意义的体重减轻[42]。一项单臂 16 周的 10 小时限时饮食研究表明，超重成年人的体重减少了 3.6%，能量摄入减少了约 20% [43]。另一项研究检查了 8 小时限时饮食的减肥功效，12 周后，肥胖成年人的体重减轻了 2.6%，能量摄入量比基线降低了约 20% [44]。最近，一项 10 小时限时饮食的单臂试验显示，12 周后代谢综合征患者体重减轻 3.0% [45]。另一项研究在肥胖成人中测试了 4 小时和 6 小时限时饮食方案，发现 8 周后两种方案产生相似的体重减轻(约 3%)，每天可减少约 550 kcal (约 30%)的能量摄入[18]。国内一项研究招募了 154 例冠心病患者，随机分为对照组和 8 小时限时禁食组，12 周后，限时禁食组的体重、脂肪量及甘油三酯均显著下降，与对照组相比差异有统计学意义[46]。

4.1.2. 有益于心脏代谢健康

除减肥外，限时饮食还可能有益于心脏代谢健康。8 小时限时饮食干预 8 周后，观察到空腹血糖，胰岛素和胰岛素抵抗明显降低[47]。4 小时和 6 小时限时饮食干预 8 周后，胰岛素抵抗均明显降低[18]。当糖尿病前驱期男性的食物摄入限制在 6 小时窗时，胰岛素敏感性和 β 细胞功能也得到改善[48]。即使没

有减肥[48]，限时饮食也可以定期降低血压[44] [45]。但是，限时饮食对血浆脂质水平的影响尚不清楚。一些研究表明甘油三酯、胆固醇或低密度脂蛋白胆固醇水平有所改善[45] [46] [47]，但另一部分研究报告限时饮食对任何脂质参数均无影响[44] [48]。

4.1.3. 降低氧化应激水平

迄今为止，限时饮食对氧化应激的影响在人类试验中进行的评估较少。5 周后，早期 6 小时限时饮食使 8-异前列腺素水平(脂质氧化应激的标志物)降低了 14% [48]。4 小时和 6 小时限时饮食干预 8 周后，8-异前列腺素水平分别降低了 36%，34% [18]。至于炎性标志物，目前的数据表明限时饮食对受试者体内的肿瘤坏死因子-α 和白介素-6 没有影响[18] [47] [48]。

4.2. 依从性

最近的几项研究评估了人类遵守限时饮食的能力。Gabel 等人[44]和 Cienfuegos 等人[18]报告了对 4、6 和 8 小时限时饮食干预出色的坚持，即在 8~12 周内受试者 80%~90%的天数在规定的窗口内进食。类似地，Kesztyus 等[49]的一项试验的参与者在 85%的天数内遵守 8~9 小时限时饮食窗。在 Martens 等[50]的研究中，在 6 周内 85%的参与者遵守 8 小时限时饮食窗，95%的参与者遵守 8.5 小时限时饮食窗。因此，在短期内(<12 周)，坚持限时饮食窗的人数似乎相当高，表明限时饮食具有较高的可行性。

4.3. 不良事件

自我报告的限时饮食不良反应较为少见。在经过 8 小时或 10 小时的限时饮食 12 周后，从基线到治疗后，恶心、便秘、腹泻、头痛、疲劳和烦躁的发生率均无明显变化[45] [51]。相比之下，早期 6 小时限时饮食导致一些轻微不良反应如呕吐、头痛、口渴和腹泻[48]。在 4 h 和 6 h 限时饮食干预 8 周的时间内，可能会出现轻度的不良反应，例如头晕、恶心、头痛和腹泻，但当参与者适应后，这些不良反应就会消失[18]。当 8 小时限时饮食与抵抗训练相结合时，据报道甲状腺激素，总三碘甲状腺素(T3)降低，略低于正常水平[47]。至于睡眠，无论是 8 小时或 10 小时的方案，都未观察到对睡眠时间或质量的负面影响[43] [52]。

5. 限时饮食的可能作用机制

1) 触发禁食的有益代谢效应

既往人体和啮齿类动物中的研究表明了禁食的各种有益的代谢效应，例如循环胰岛素和瘦素水平降低、胰岛素敏感性增加、脂肪酸氧化增加、脂肪蓄积减少以及促炎性细胞因子和氧化应激标记物水平降低[48] [53]-[58]。肝细胞通过产生酮体来对禁食做出反应，酮体可作为葡萄糖和脂肪酸的替代代谢燃料维持个体生理需求[59]。此外，酮类(特别是 β-羟基丁酸)的信号传导特性会诱导许多酮类介导的表观遗传转变，包括自噬诱导、昼夜节律调节以及各种表观遗传调控[60] [61]。

2) 恢复昼夜的饮食禁食节律

每天定期的禁食还可能恢复昼夜的饮食禁食节律来调节细胞的新陈代谢。在哺乳动物中，下丘脑视交叉上核(Suprachiasmatic nucleus，SCN)是内源性昼夜节律的主要产生者，并起着调节周围系统的主时钟作用[62]。SCN 的昼夜节律时钟与感光性视网膜神经节细胞的光信号同步，通过视网膜下丘脑束，并优化昼夜代谢效率[63]。SCN 神经元发出 24 小时有节奏的信号，即昼夜节律时钟，该信号通过转录和翻译反馈回路进行调节。SCN 通过下丘脑连接控制昼夜睡眠觉醒行为，并与其他大脑区域和周围组织(包括肝脏，胰腺、肠道、肌肉和脂肪组织)的周围时钟同步，从而产生 24 小时的新陈代谢[64] [65]。SCN 主要通过光同步，而进食/禁食周期是周围时钟的主要同步器。因此，不规则的进食时间会导致周围时钟发生偏

移，导致中央时钟与周围时钟之间的不同步，从而导致代谢紊乱[66]。因此新兴的限时饮食通过限制进食时间可能会减少中央时钟与周围时钟之间的不同步，并恢复受损的代谢途径。

3) 调节肠道微生物的组成

有研究表明限时饮食可能通过将肠道微生物改变为致肥胖性较低的微生物来影响宿主代谢[67]。当给动物饲喂高脂饮食时，限时饮食似乎能恢复涉及营养吸收的几个细菌的昼夜变化[68]。Chaix 等[67]的研究中，限时饮食恢复了乳杆菌和乳球菌家族的昼夜变化，据推测可以防止肥胖的代谢后果。随意喂养和限时饮食小鼠粪便的代谢组学分析显示出显著差异，这可能解释了限时饮食小鼠所见的某些改善[68]：饮食中的半纤维素通常被肠道微生物分解为木糖和半乳糖，其中一些被宿主吸收，相对于随意喂养的小鼠，限时饮食小鼠的粪便中排泄出更多的木糖和半乳糖，这表明限时饮食降低了宿主对这些简单糖的吸收；通常，很大一部分胆汁酸会从肠道中重新吸收，限时饮食小鼠粪便中胆汁酸水平升高表明限时饮食小鼠肝脏和血清胆固醇水平的降低可能是由于粪便中胆汁酸的净清除所致。

6. 小结与展望

精神分裂症和抗精神病药物可能通过破坏机体昼夜节律的平衡、增加食欲从而增加食物摄入、增加胰岛素抵抗和各种炎症反应，改变人类肠道微生物组的组成等机制来导致代谢紊乱的发生。而限时饮食不仅可以通过缩短每日的进食时间而减少食物摄入，还可以通过稳定每日的进食/禁食时间来调节中央时钟和周围时钟之间的同步而恢复昼夜节律的平衡。限时饮食由于禁食时间相对较长，还会触发禁食的各种有益代谢效应，可能降低胰岛素抵抗、炎症反应等。另外，限时饮食也可以通过调节肠道微生物组的组成和代谢从而影响宿主代谢。由此可见，精神分裂症和抗精神病药物引起代谢紊乱的机制和限时饮食产生有益代谢作用的机制之间存在较多的关联，所以如果把限时饮食应用于存在代谢紊乱的精神分裂症患者人群中，很可能会产生显著的代谢改善效果。因此，限时饮食可能是改善精神分裂症患者代谢问题的新兴干预措施。未来的研究，一方面可以尝试把限时饮食应用于存在代谢紊乱的精神分裂症患者人群中，以观察限时饮食是否会产生有益的代谢效果，另一方面可以探索限时饮食是否扭转了精神分裂症患者异常的微生物组代谢从而产生了有益的代谢作用。

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